Immune and metabolic remodeling following bariatric surgery: Implications for targeted immunotherapy (Review)

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Abstract. Over the past few years, bariatric surgery has emerged as a potent remedy for obesity and its related metabolic issues, with its effects on peripheral immune cells garnering considerable attention. Obesity, recognized as a chronic metabolic condition, is intricately connected to dysfunctions spanning a range of immune cell types. Among peripheral immune cells, T cells, B cells and monocytes, obesity markedly alters their counts and functions, driving the inflammation and metabolic dysfunction characteristic of the condition. The modifications in these immune cell cohorts are inextricably intertwined with the augmentation of postoperative metabolic functions and have the potential to exert a salutary effect on complications associated with obesity. The present review primarily examined the latent influence of bariatric surgery on the number and function of peripheral immune cells, thereby offering novel perspectives and therapeutic targets for the immunotherapy of obesity.

Contents

1. Introduction

Obesity has now become the world's most significant public health issue, intimately intertwined with an assortment of metabolic dysregulations, encompassing insulin resistance, type 2 diabetes mellitus and cardiovascular pathologies (1). Over the past few years, there has been a burgeoning interest in the role of immune cells in obesity and its associated pathologies, which has risen to prominence as a pivotal area of investigation (2).

Bariatric surgery, recognized as an effective intervention for obesity and its associated metabolic disorders, has become widely utilized in clinical settings (3). Research indicates that the peripheral immune cells of obese individuals experience substantial alterations prior to and following bariatric surgery (4). The observed alterations pertain to the restructuring of immune cell populations, alterations in their activation levels and changes in the expression patterns of molecules that regulate immune checkpoints (4). Bariatric surgery is known to elicit transformations in the circulation of T cells among obese individuals, notably affecting the regulatory dynamics of cluster of differentiation (CD)4^+ and $CD8^+$T cell populations. Additionally, alterations in the gut microbiome following bariatric surgery may influence the progression of obesity-related diseases by modulating the host's immune system (5).

Nevertheless, research into the changes in peripheral immune cells following bariatric surgery remains an area of

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Abbreviations: CCR5, C-C chemokine receptor type 5; CD, cluster of differentiation; CRP, C-reactive protein; DC, dendritic cell; FAO, fatty acid oxidation; FXR, farnesoid X receptor; GPR97, G-protein coupled receptor 97; HIF-1α, hypoxia-inducible factor-1 alpha; HK2, hexokinase 2; IL, interleukin; iNKT, invariant natural killer T; LDH-A, lactate dehydrogenase A; MDSC, myeloid-derived suppressor cell; NET, neutrophil extracellular trap; NK, natural killer; NKT, natural killer T; NLR, neutrophil-to-lymphocyte ratio; OXPHOS, oxidative phosphorylation; PD-1, programmed death-1; PI3K, phosphoinositide 3-kinase; Tfh, T follicular helper; Th, T helper; TNF, tumor necrosis factor; Treg, regulatory T cell; VAT, visceral adipose tissue

Key words: bariatric surgery, peripheral immune cells, obesity, inflammation, targeted therapy

ongoing exploration and refinement (6). Variations in sample selection, detection methods and observation time across different studies have contributed to some inconsistencies in the findings. Moreover, the causal link between changes in immune cells and the improvement of obesity-related diseases, as well as the underlying molecular mechanisms, remain incompletely understood (7). The risk of complications following bariatric surgery can now be quantified by four categories of biomarkers: Pre-operative albumin <3.5 g/dl increases 30-day mortality and anastomotic leak risk by 1.4-2.3-fold (8); C-reactive protein (CRP) >12 mg/dl plus white blood count >12x10^9/l on post-operative day 1 yields an 82% positive predictive value for major complications (9); rising oxidative-stress markers [malondialdehyde (MDA), 8-hydroxy-2'-deoxyguanosine (8-OHdG)] and interleukin (IL)-6 peaks show a dose-response relationship with Clavien-Dindo ≥III complications (8); and pre-operative deficiencies in Fe, B12 and 25-hydroxy vitamin D affect 35-60% of patients, with a 25% anemia rate at one year, indicating that peri-operative inflammatory and nutritional biomarkers jointly forewarn of both early and late adverse events (10).

The present review sought to comprehensively synthesize the latest research advances regarding the changes in peripheral immune cells following bariatric surgery. It aims to investigate the underlying links between these immune cell alterations and obesity-related diseases and to suggest potential directions for future research. By doing so, it hopes to offer a new theoretical foundation and innovative research perspectives for the management of obesity and its associated conditions.

2. Peripheral immune cells prior to and following bariatric surgery

Lymphocytes

T cells. Immune cell populations in patients with obesity are shown in Fig. 1. In T cells, the T helper (Th)1 cells in patients with obesity have a higher level of activation and a lower level of programmed cell death protein 1 (PD-1) expression (11). The proportions of Th17 and Th1/17 cells are increased (12). $CD4^+$ regulatory T cells (Tregs) shift towards Th1 and Th1/17-like phenotypes, accompanied by elevated C-C chemokine receptor type 5 (CCR5) expression (13). In the $CD4^+$T cell subset, obese mice exhibit a substantial rise in Th17 cells that express the effector cytokines IL-17A and IL-17F. This finding indicates that obesity might alter the inflammatory profile from being Th2-mediated to Th17-dominant (7). Obesity leads to exhaustion of $CD4^+$T cells and faster cellular aging (14). Indeed, the condition of obesity has been associated with the demise of regulatory T lymphocytes within adipose tissue, which in turn can disrupt the equilibrium of the immune system and diminish insulin responsiveness (15).

Following bariatric surgery, there is a noted augmentation in the population of $CD4^+$T lymphocytes and the $CD4^+$T cell profile returned to a phenotype resembling that of lean controls, along with an expansion of T follicular helper (Tfh) cells. However, no changes were noted in $CD8^+$T cells (4). Bariatric surgery altered the subset composition of $CD4^+$T cells and B cells to more closely resemble that of lean controls. Furthermore, there was an enhancement in the capacity of $CD4^+$T cells to synthesize IL-2 and IFN-γ, observed three months following the surgical procedure. Nonetheless, the cytokine production capabilities of $CD8^+$T cells and B cells did not exhibit any significant alteration three months post-operation (16). However, while reviewing the literature, it was found that this study indicated a significant increase in the number of $CD8^+$T cells following bariatric surgery (4,6). Therefore, the key reason for the divergent conclusions lies in the different metrics used: One study focused on the relative proportion of cells within lymphocytes, whereas others monitored the absolute count in blood (4,6,16). Post-surgical weight loss and hemoconcentration can raise the total number of cells while keeping their proportion among lymphocytes unchanged.

Obesity disrupts the subset of regulatory T cells that provide metabolic protection in visceral adipose tissue (VAT), leading to heightened VAT inflammation and aggravated insulin resistance (17). Regulatory T cells (Tregs) gather in VAT to sustain systemic metabolic balance, but their numbers decrease during obesity; restoring Treg cholesterol homeostasis was found to rescue VAT Treg accumulation in obese mice (15). Patients with low Treg levels showed more significant metabolic improvement after surgery, likely due to their more severe preoperative inflammatory state (18). After the removal of inflammatory adipose tissue during surgery, the proportion of Tregs in the remaining fat tissue may increase relatively, though further research is needed to confirm this (19).

B cells. In B cells, the adipose tissue size in obese individuals grows with age, causing systemic and intrinsic B cell inflammation (20). This leads to a decline in protective B cell responses and an upsurge in pathogenic B cell responses, which in turn results in increased secretion of autoantibodies (20). In addition, obese individuals experience heightened IL-6 production and diminished IL-10 production. Furthermore, immune activation markers like tumor necrosis factor (TNF)-α and micro-RNAs are found to be elevated in stimulated B cells and these alterations are inversely associated with B cell function (21). At 6 months post-bariatric surgery, patients exhibited a unique B cell profile that is nearly unrecognizable compared with their preoperative state and is somewhat similar to that of healthy lean individuals (22). Despite overall improvements in inflammation and metabolic health, discrepancies within the B cell compartment in comparison to lean controls continue to be observed (22).

Following bariatric surgery, the ability of B cells to produce cytokines in patients with obesity stays at levels comparable to those before the surgery and does not reach the levels seen in healthy individuals (16). This alteration in function might be linked to the persistent inflammation often seen in obesity. Even though bariatric surgery helps reduce inflammation, it may take B cells a longer time to regain full function (16). Thus, the juxtaposition of 'structural similarity' with 'functional non-recovery' is not contradictory; rather, it reflects the staged nature of post-surgical immune remodeling: First achieving 'form', then 'function', with the latter requiring a more prolonged period of inflammation resolution.

Natural killer (NK) cells. Among obese individuals, there is a decline in the expression of activating receptors on NK cells, while inhibitory receptors on NK cells are more highly

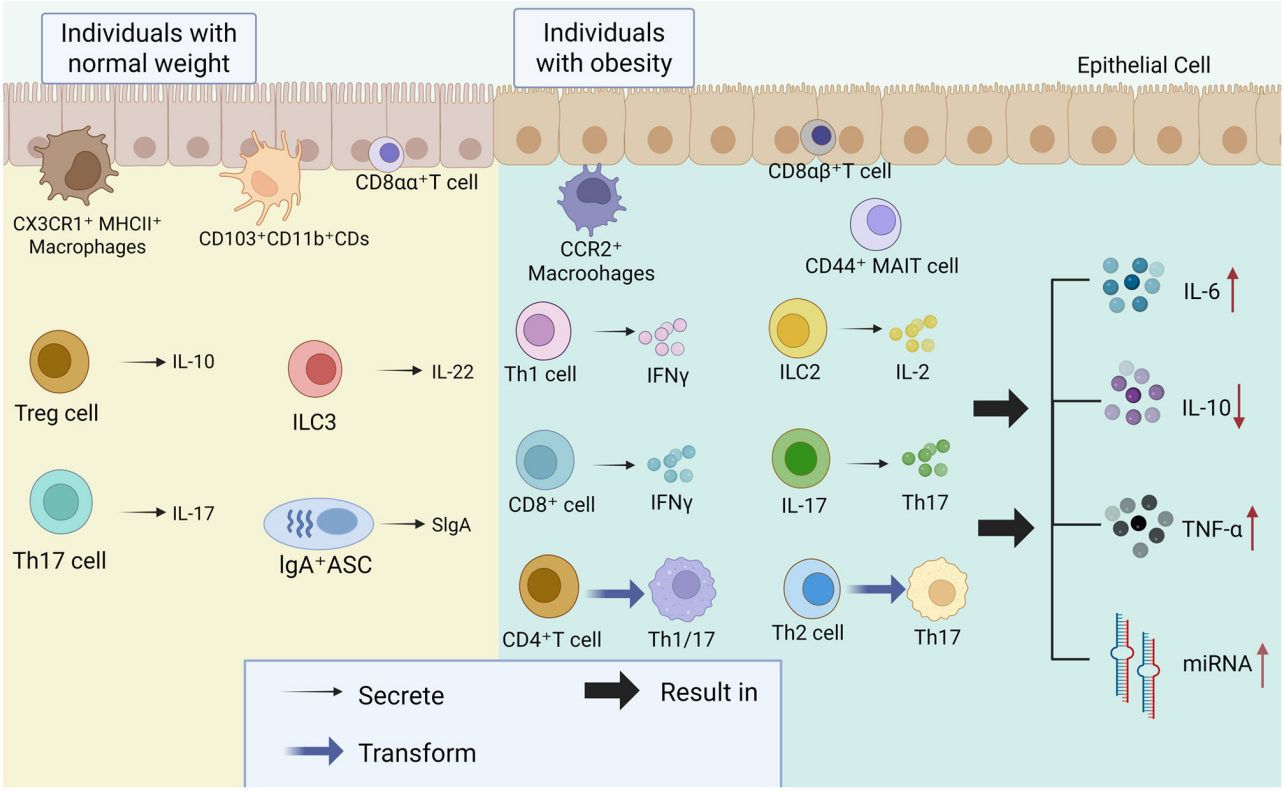

Figure 1. The changes in the composition and function of immune cells in the gut under normal and obese conditions. CX3CR1, C-X3-C motif chemokine receptor 1; MHCII, major histocompatibility complex class II; CD, cluster of differentiation; Treg, regulatory T cell; Th, T helper; IL, interleukin; ILC, innate lymphoid cells; IgA, immunoglobulin A; ASC, antibody-secreting cell; CCR2, C-C chemokine receptor 2; MAIT, mucosal-associated invariant T; miRNA, microRNA.

expressed. In addition, studies have shown that in the natural killer cells of overweight and obese subjects, the expression of the maturation and differentiation marker CD27 is found to be insufficient (23). Additionally, the functionality of natural killer cells is markedly diminished in both obese animals and humans (24). In obesity, human adipose tissue-resident NK cells exhibit a wide range of phenotypic variations (25).

The CD56+NK cell subset exhibit an increase immediately following surgery (0 h), with its characteristic genes primarily enriched in biological processes such as the Jak-STAT signaling pathway and cell adhesion molecules (at 24 h), as well as carbon metabolism (at 48 h) (26). This suggests that bariatric surgery might enhance NK cell function through the regulation of their metabolism and signaling pathways. While reviewing the relevant literature, a study was found indicating that following surgery, the number of NK cells may further decrease and does not recover to a healthy level even 9-11 months following surgery (27). Ultimately, The present study found that while the surgery itself causes a transient suppression of NK cells (a short-term decrease), bariatric surgery, by treating obesity, fundamentally improves health, leading eventually to the recovery and even expansion of NK-cell numbers (a long-term increase). Thus, these outcomes are not contradictory.

Natural killer T (NKT) cells. NKT cells are capable of detecting lipid antigens displayed by cells that express CD1d (28). Within adipose tissue, they interact with a variety of CD1d-expressing cells, such as adipocytes, macrophages and dendritic cells. Through these interactions, NKT cells play a pivotal role in orchestrating either a pro-inflammatory or anti-inflammatory environment. This environment, in turn, has a significant effect on the progression of obesity and insulin resistance. The intricate interactions of NKT cells within adipose tissue help to shape a specialized microenvironment that exerts influence over both obesity and insulin resistance. A study revealed that, compared with healthy individuals, the body weight and waist circumference of patients with obesity do not affect the proportion of invariant (i)NKT cells (29). However, excessive intake of free sugars can diminish the levels of iNKT cells, thereby leading to immune dysfunction. Particularly, free sugars from solid foods can reduce the proportion of iNKT cells by 22% (29). The abundance of NKT cells and iNKT cells markedly escalates subsequent to bariatric surgery, which implies that these interventions might ameliorate obesity-associated metabolic derangements through the recalibration of immune cells residing in adipose tissue (30).

Myeloid cells

Monocyte-macrophage. In individuals with obesity, there is a notable rise in the quantity of monocytes present in the peripheral blood (31-33). These monocytes are marked by a high rate of glycolysis and markedly higher mitochondrial oxygen consumption (32). Additionally, such changes may result in abnormal cytokine secretion, including elevated levels of IL-8 (32). Conversely, the recruited monocytes tend to differentiate into M2 macrophages, which in turn amplifies the inflammatory response (33). Following bariatric surgery, the

phenotypic alterations of monocytes, including the proportion of $CCR5^+$ monocytes, showed improvement, yet they did not completely revert to normal levels (4). Post-bariatric surgery, the frequency of $hCD7^+$ monocytes in peripheral blood exhibited a negative correlation with regaining weight (31). Among those who achieved weight loss and sustained it, a higher proportion of $hCD7^+$ monocytes was observed, whereas individuals who experienced weight regain had a lower proportion (31). Following bariatric surgery, monocytes in adipose tissue still retain certain pro-inflammatory characteristics, which may serve as a potential mechanism underlying weight regain and metabolic disorders (34).

Macrophages associated with lipids, known as LAMs, release the cytokine transforming growth factor-β1. This factor, via interaction with aldehyde dehydrogenase 1 family member A1, instigates a loss of brown adipocyte characteristics and facilitates the metamorphosis of brown adipose tissue into white adipose tissue, a phenomenon often observed in conditions such as obesity and type 2 diabetes (35). Extracellular vesicles released by bone marrow macrophages in obese mice can lead to bone loss in lean mice by enhancing fat formation and suppressing bone formation through the regulation of skeletal stem/progenitor cells (36). Moreover, a newly identified subset of adipose tissue macrophages, termed interstitial adipose-tissue macrophages (iMAMs) has been discovered using single-nucleus RNA sequencing (37). These iMAMs display traits of inflammatory and metabolic activation, where protein disulfide-isomerase A3 plays a key role in sustaining their migratory and pro-inflammatory functions (37). Following bariatric surgery, there is a reduction in the number of pro-inflammatory macrophages within adipose tissue, whereas the count of anti-inflammatory macrophages, such as M2 macrophages, increases (38). This alteration aids in diminishing the inflammatory condition of adipose tissue and enhancing metabolic status (38). Despite the reduction in pro-inflammatory macrophages following bariatric surgery, the inflammatory gene expression levels, including those of TNF and IL-6, persist at higher levels than those observed in individuals who are healthy (34).

Obesity has the potential to amplify the functional activity of myeloid-derived suppressor cells (MDSCs) (39-41). Obesity triggers the upregulation of PD-1 on macrophages, leading to the suppression of anti-tumor immunity (39). Furthermore, obesity drives the expansion of MDSCs in ovarian cancer by elevating IL-6 production, which strengthens the tumor's capacity to evade immune detection (41). However, it is regrettable that there is still a lack of research on myeloid-derived suppressor cells following bariatric surgery.

Mast cells. In obese individuals, there is a marked elevation in the mast cell count within adipose tissue (42,43). Additionally, these mast cells become activated and show a positive correlation with indicators of fibrosis, inflammation and diabetes (42). By releasing a cascade of inflammatory cytokines, chemokines and proteolytic enzymes, these cells foster both angiogenesis and apoptosis within adipose tissue, this dual action exacerbates the conditions of obesity and glucose intolerance (43). Adipocytes release adipokines such as leptin and adiponectin, which modulate mast cell activity. Although both substances can induce the migration of mast cells, leptin amplifies the release of histamine and cysteinyl leukotrienes, along with the expression of chemokine cc motif ligand 2, while adiponectin, conversely, encourages the generation of the anti-inflammatory cytokine IL-10. This demonstrates how obesity drives chronic inflammation by altering mast cell behavior (44). Indeed, the major tissue injury during surgery itself is the heart and relevant biomarkers reflect this: In heart failure, the heart's capacity to generate energy via oxidative phosphorylation (using oxygen) is impaired, forcing it to rely more heavily on glycolysis or other metabolic pathways. Bariatric surgery may alleviate mast cell (MC)-driven inflammation through the following pathways: reducing adipocyte stress→decreasing MC activation; improving the adipokine profile (such as lowering leptin and increasing adiponectin)→inhibiting MC-mediated cytokine release; remodeling the immune microenvironment of adipose tissue→reducing MCs in visceral fat after surgery (45).

Dendritic cells. In mice undergoing high-fat diet and fecal microbiota transplantation linked to obesity, the differentiation of bone marrow precursor cells into MDSCs is enhanced, whereas their potential to develop into dendritic cells (DCs) is reduced (46). This indicates a decline in dendritic cell populations in individuals with obesity (47). Moreover, in obese mice, $CD103^+$ DCs in the mesenteric lymph nodes exhibit elevated expression of dipeptidyl peptidase-4 and TNF-α, potentially influencing Treg expansion and directly causing Treg loss via interactions with cyclophilin A (47). Post metabolic surgery, there is observed a significant elevation in the proportion of myeloid dendritic cells within the peripheral blood circulation of patients with obesity, with these levels eventually gravitating towards normalization after the surgical intervention (48). Following the operation, the total count of peripheral blood DCs dropped in both patient groups but later recovered. In the open surgery group, the proportion and activation level of tolerogenic DCs were relatively lower, whereas the proportion of immature dendritic cells was comparatively higher (49).

Granulocytes

Neutrophils. Diet-induced obese mice show earlier infiltration of neutrophils and enhanced formation of neutrophil extracellular traps (NETs) during the process of fracture healing (50). NETs can hinder the process of bone healing by activating the NOD-like receptor family pyrin domain containing 3 inflammasome. The activation process exerts a dual effect on the cellular landscape, simultaneously inhibiting the osteogenic differentiation of bone marrow mesenchymal stem cells and driving macrophages toward the M1 polarization phenotype, a hallmark of pro-inflammatory activity (50). A strong positive correlation exists between neutrophil count and measures of body mass index, triglycerides and uric acid levels (51). Transformations in the peripheral immune cell composition post-bariatric surgery are shown in Fig. 2. Bariatric surgery markedly affects neutrophil populations, with low-density neutrophils showing a substantial reduction within months following the procedure (52). The dynamic changes in the neutrophil-to-lymphocyte ratio (NLR) following bariatric surgery reveal a significant decline in NLR within 3 months post-surgery, driven by a more marked reduction in neutrophil counts compared with lymphocytes (53).

Eosinophils. In patients with obesity, a decrease in eosinophils within adipose tissue, or their complete absence as seen

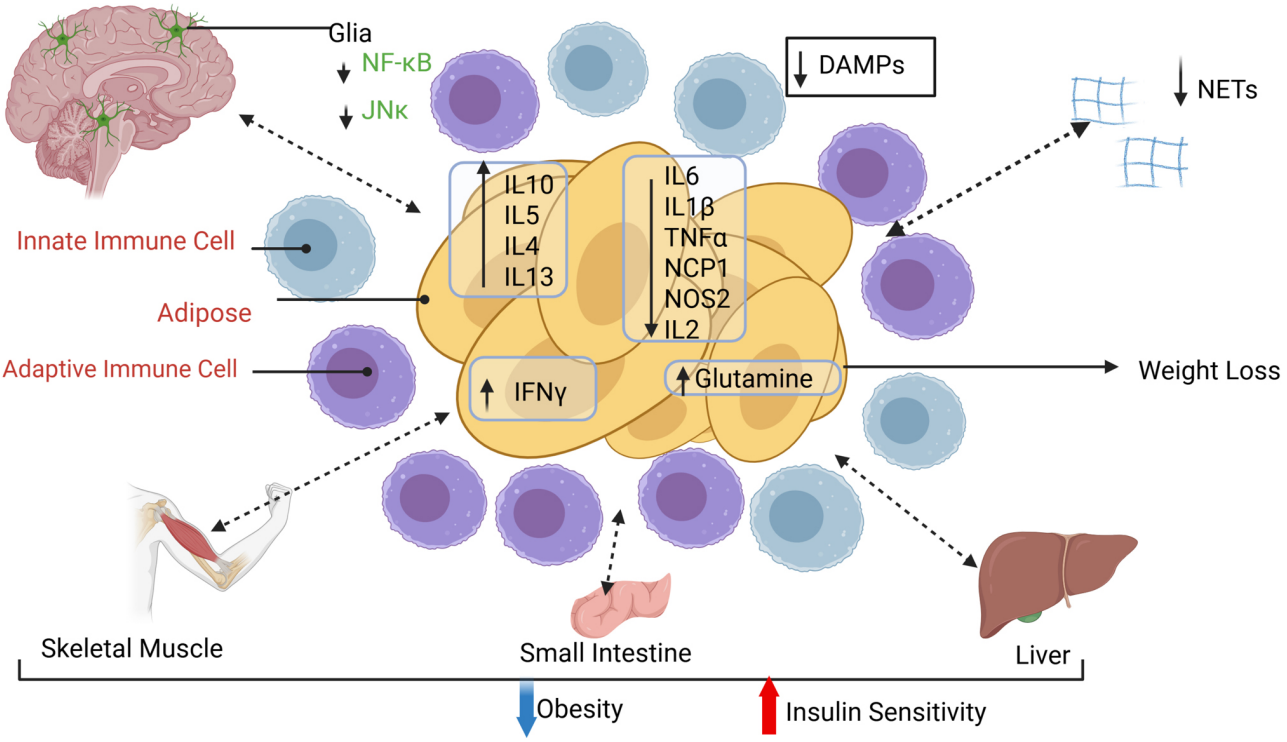

Figure 2. How bariatric surgery influences multiple organs such as the brain, adipose tissue, skeletal muscle, small intestine and liver by affecting immune cells and factors, ultimately leading to weight loss and increased insulin sensitivity. DAMPS, damage-associated molecular patterns; NETs, neutrophil extracellular traps; IL, interleukin; NOS2, nitric oxide synthase 2; TNF, tumor necrosis factor; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor-κB; IFN, interferon.

in ΔdblGATA knockout mice, results in elevated body weight and worsened insulin resistance (54,55). Eosinophils enhance the browning and thermogenic activity of adipose tissue by releasing Th2-type cytokines, including IL-4 and IL-13 (55). However, excessive activation of the Th2 response in the liver can contribute to fibrosis and the progression of liver disease (54). Investigations into the efficacy of bariatric interventions among subjects afflicted with eosinophilic esophagitis have demonstrated that procedures such as the Roux-en-Y gastric bypass and sleeve gastrectomy are notably successful in facilitating considerable weight reduction. Moreover, these surgical interventions do not lead to an increase in the severity of eosinophilic esophagitis symptoms following the operations (56). However, direct evidence on eosinophil changes remains scarce, suggesting that bariatric surgery could potentially benefit eosinophil-related inflammatory diseases.

3. Immune pathway therapy following bariatric surgery

Studies have delineated the sophisticated interplay among bariatric surgery, metabolic well-being and the modulation of the immune system. Evidence suggests that adiponectin exerts an anti-inflammatory effect by suppressing the expression of TNF-α, a mechanism that could be instrumental in the metabolic shifts and inflammatory responses observed post-bariatric surgery (57). Additionally, it has been established that obesity may dampen anti-tumor immunity by elevating PD-1 expression on macrophages, implying that bariatric surgery could potentially augment the immune system's tumor-combating prowess through the modification of this pathway (58).

The prospect of harnessing the immune microenvironment linked to obesity for the advancement of cancer therapies has been studied within the scientific community (59). Discussions have centered on the potential to target the immune milieu in obese individuals to refine cancer treatments, a process that may be markedly influenced by the alterations prompted by bariatric surgery (59). Moreover, investigations have probed the impact of obesity and adipose tissue on T-cell responses and the efficacy of cancer immunotherapy through immune checkpoint inhibitors, indicating that bariatric surgery could potentially alter the dynamics between adipose tissue and T-cells, thereby enhancing the impact of immunotherapeutic interventions (60). Bariatric surgery markedly improves immunotherapy response through several converging immune mechanisms: Post-operative restoration of peripheral Tregs, expansion of Tfh cells and downregulation of PD-1 relieve T-cell suppression (4). Concomitant reduction of PD-1^{+} macrophages and MDSCs remodels the tumor microenvironment, converting 'cold' into 'hot' tumors (59). A systematic review confirmed polarization from Th1/Th17 toward Th2/Treg profiles with decreased IL-17 and IFN-γ, thereby enhancing checkpoint-inhibitor sensitivity and increased Breg cells secreting IL-10 and TGF-β, further dampening pro-inflammatory responses (61). Additionally, recovery of MAIT-cell frequencies and diminished IL-17 indicate reprogramming of the metabolic-immune axis that synergistically strengthens anti-tumor immunity (62).

Furthermore, the intricate effects of obesity on T-cell functionality during tumor progression and immune checkpoint blockade have been subjected to intense examination,

Table I. Comparative immunological outcomes of weight-loss interventions and key biomarkers.

Authors, year	Method/biomarker	Immunological effects	(Refs.)
Chen *et al*, 2013	Pharmacologic weight loss	GLP-1 receptor agonists (e.g., liraglutide) ↓systemic CRP, TNF-α, IL-6 and ↑ adiponectin after ≥5% weight loss.	(65)
Mehrdad *et al*, 2021	Dietary restriction	10% weight loss via 600 kcal deficit + orlistat ↓circulating natural-killer (CD16/56+) cells in obese women, suggesting weakened antiviral immunity.	(66)
Ji *et al*, 2025	Ketogenic diet	4-week high-fat, low-carbohydrate diet adipose-tissue TNF-α and IL-6 gene expression despite weight loss; no change in systemic CRP.	(67)
Nemet *et al*, 2011	Exercise training	12-week endurance exercise anti-inflammatory adiponectin and visceral adipose CCL2 in both sexes; men display greater IL-10 rise than women.	(68)
Zhu *et al*, 2022	Age	Adults ≥60 years lose more weight than younger peers after identical lifestyle intervention, but show smaller reductions in HbA1c and CRP, indicating reduced anti-inflammatory benefit.	(69)
Potenza *et al*, 2016	Sex	Women lose less weight than men after calorie restriction and exhibit smaller improvements in CRP and IL-6, partly explained by preservation of fat-free mass and sex-hormone-driven immune modulation.	(70)

GLP-1, glucagon-like peptide-1; CRP, c-reactive protein; TNF, tumor necrosis factor; IL, Interleukin; CD, cluster of differentiation; CCL2, chemokine cc motif ligand 2; Hb1Ac, glycated hemoglobin.

underscoring the necessity for a more nuanced comprehension of how bariatric surgery could influence these interactions by modulating T-cell functions to refine immunotherapeutic strategies (63). To a greater extent, the administration of gut-targeted therapies, such as probiotics and prebiotics, can markedly optimize the health of the gut microbiota, thereby augmenting the integrity of the intestinal barrier and exerting a regulatory effect on immune responses (64).

According to current research, there are significant differences in immune responses to various weight-loss strategies (pharmacological, dietary and exercise interventions) and to biological markers such as age and sex. The differences are showed in Table I (65-70).

Metabolic pathways

Glycometabolism. Glycolysis is one of the most studied metabolic pathways in immune cells, with its high metabolic flux being a hallmark of activated immune cells, especially in pro-inflammatory immune cells (71). Hypoxia-inducible factor-1α (HIF-1α), a key subunit of HIF-1, is activated in hypoxic environments and can upregulate glycolysis in immune cells (72). Moreover, it exerts a substantial influence on oxidative stress, cancer progression and a myriad of other diseases (72). Research has demonstrated that inhibiting HIF-1α can effectively diminish glycolysis in immune cells, including macrophages and T cells (73). This finding suggests a promising therapeutic strategy for addressing autoimmune diseases, metabolic disorders and various inflammatory conditions.

Within the intricate landscape of immunometabolic regulation, the phosphoinositide 3-kinase (PI3K)/Akt signaling cascade emerges as a pivotal actor orchestrating glycolysis within immune cells, exerting its influence through downstream effectors such as 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) and glucose transporter type 1 (74-76). PFKFB3, a sentinel enzyme governing glycolytic flux, is subject to activation by the PI3K/Akt axis, thereby amplifying the glycolytic program (78). This metabolic amplification can be attenuated by specific PFKFB3 inhibitors, which have demonstrated efficacy in diminishing both glycolysis and the pro-inflammatory vigor of immune cells (74-76).

Moreover, the interplay between fatty acid oxidation (FAO) and glycolysis in $CD4^+$T cells reveals a complex regulatory nexus (78). Elevated FAO has been implicated in inducing glycolysis in these cells, thereby fueling their activation and pro-inflammatory effector functions (78). This metabolic interplay presents a viable therapeutic target, with inhibitors of CPT-1, such as DC-Gonib32, demonstrating the ability to dismantle the aberrantly upregulated glycolysis in $CD4^+$T cells within obese murine settings (78). Collectively, these advances underscore the potential of strategically targeting glycolysis and associated metabolic pathways as a means to recalibrate immune cell function and mitigate inflammatory pathologies.

In the aftermath of bariatric surgery, patients undergo substantial metabolic transformations that are inextricably linked to glycolysis. The elevation of bile acid levels post-surgery precipitates the activation of receptors such as TGR5 and farnesoid X receptor (FXR), thereby exerting a profound influence on glycolytic metabolism (79). For example, the activation of TGR5 catalyzes the secretion of glucagon-like peptide-1, which in turn modulates glucose

metabolism (79). Concurrently, an enhancement in insulin sensitivity is observed, as evidenced by the upregulation of hepatic lipid oxidation gene expression and the downregulation of lipogenic gene expression, both of which have a significant impact on glycolysis (79). These metabolic modifications present novel avenues for targeted therapeutic interventions following bariatric surgery.

In the realm of oncology, the metabolic alterations elicited by bariatric surgery may have a substantial effect on the glycolytic metabolism of tumor cells. Extant research posits that tumor cells predominantly engage in aerobic glycolysis as a means of metabolic reprogramming (80). By targeting glycolysis-related metabolic enzymes, such as lactate dehydrogenase A (LDH-A) and hexokinase 2 (HK2), it is possible to curtail tumor progression (80). For instance, the inhibition of LDH-A results in a reduction of lactate production, which subsequently mitigates immune suppression and fortifies anti-tumor immune responses (80). Moreover, post-surgery improvements in pancreatic β-cell function lead to more efficient and coordinated insulin secretion. The regulation of glycolysis can further optimize insulin secretion and enhance glucose control (79).

Strategies for glycolysis-targeted treatment encompass the development of specific metabolic enzyme inhibitors, such as those targeting LDH-A and HK2, to suppress tumor cell glycolysis, diminish lactate production and augment anti-tumor immune responses (81). Additionally, modulating bile acid levels or activating bile acid receptors like TGR5 and FXR can indirectly influence glycolytic metabolism, thereby improving glucose control and insulin sensitivity. The potential applications of these strategies merit further exploration (79).

Modulation of oxidative phosphorylation. Therapeutic targeting of immunometabolism offers a novel approach to treat various diseases, including cancer, autoimmune disorders and inflammatory conditions (82). Several strategies have emerged from preclinical and clinical studies. Modulation of oxidative phosphorylation (OXPHOS) is one such strategy. Downregulating OXPHOS in immune cells, particularly in Tregs has shown potential in cancer immunotherapy. For instance, targeting FABP5 to reduce OXPHOS in Tregs can impair their immunosuppressive function, enhancing anti-tumor immunity (83). Similarly, OXPHOS inhibitors such as IACS-010759 have demonstrated efficacy in targeting cancer cells with high Myc activity, although the exact mechanism remains unclear (84,85). Conversely, upregulating OXPHOS in immune cells, such as $CD8^+$T cells, can improve their anti-tumor activity. For example, incorporating the 4-1BB domain into chimeric antigen receptor T cells upregulates OXPHOS, leading to enhanced persistence and efficacy in cancer immunotherapy (86). Additionally, drugs like NX-13, which upregulate OXPHOS, have shown anti-inflammatory effects in ulcerative colitis (87,88).

In the realm of cancer therapeutics, the inhibition of glycolysis in immune cells has garnered significant attention. However, given the immunosuppressive milieu that characterizes the cancer microenvironment, the strategy of inhibiting immune cell glycolysis in cancer, excluding immune cell-derived tumors, requires nuanced consideration. JHU083, a glutamine antagonist, exemplifies a dual-action inhibitor capable of suppressing glycolysis in both tumor cells and effector $CD8^+$T cells (89). Intriguingly, the reduction of glycolysis in $CD8^+$T cells precipitates an upregulation of OXPHOS, thereby activating potent anti-tumor immune responses (89,90). This phenomenon is inextricably intertwined with the replenishment of tricarboxylic acid cycle intermediates, a mechanism that has been thoroughly investigated and elucidated (90).

In a similar vein, L-arginine imitates the effects of glutamine antagonists by catalyzing a metabolic transition from glycolysis to OXPHOS in effector T cells, thereby enhancing their anti-tumor efficacy (91). HK2, a crucial rate-limiting enzyme in the glycolytic pathway, has garnered significant attention as a potential therapeutic target in cancer treatment (92). The inhibition of HK2 has been shown to suppress glycolysis, thereby disrupting the expression of PD-L1 and subsequently reactivating $CD8^+$T cells (93). In summary, rather than merely suppressing inflammation, glycolysis inhibitors have exhibited anti-tumor immune effects by enhancing OXPHOS. This phenomenon is likely due to the non-specific targeting of glycometabolism in immune cells by existing inhibitors. In the aftermath of bariatric surgery, adipose tissue undergoes a marked enhancement in mitochondrial function, characterized by an upregulation of gene expression associated with OXPHOS (94). This, in turn, amplifies the oxidative capacity of adipose tissue, facilitating fatty acid oxidation and energy expenditure. These metabolic alterations not only contribute to weight reduction but also exert a salutary effect on insulin sensitivity and overall metabolic health. Furthermore, obesity is frequently accompanied by mitochondrial dysfunction, a condition that bariatric surgery can effectively ameliorate by diminishing mitochondrial fragmentation and bolstering mitochondrial OXPHOS function (95). In the context of oncology, OXPHOS emerges as a pivotal metabolic vulnerability for certain tumor subtypes, such as lung cancer cells harboring SWI/SNF mutations and prostate cancer cells with PTEN deficiency, as these cells are highly reliant on OXPHOS for their proliferation and survival, OXPHOS inhibitors, including Gboxin and berberine, have been demonstrated to exert a potent inhibitory effect on tumor growth (96,97). Additionally, the OXPHOS activity of tumor cells in obese individuals may be attenuated due to the improved mitochondrial function, thereby reducing the recurrence rate of tumors. Consequently, targeting OXPHOS presents a novel and promising therapeutic strategy for drug-resistant tumors, offering the potential to enhance anti-tumor efficacy (95). The present review posits that these findings furnish a theoretical foundation for the development of therapeutic strategies targeting OXPHOS, which holds promise for playing a significant role in the treatment of metabolic disorders and oncology.

Lipid metabolism. Lipid metabolism modulation is another area of interest. Modulating fatty acid oxidation (FAO) in immune cells has been explored in common diseases, including cancer, autoimmune diseases, metabolic disease, atherosclerosis and lung inflammation (78,86,98-105). Downregulating FAO in M2 macrophages can alleviate immunosuppression in cancer, while upregulating FAO in macrophages can promote anti-inflammatory effects in conditions like ulcerative colitis (105). peroxisome proliferator-activated receptor α activators, such as fibrates, have shown promise in enhancing FAO and reducing

inflammation. Inhibiting lipid synthesis in immune cells, particularly in Tregs and $CD8^+$T cells, has been shown to suppress immunosuppression and pro-inflammatory responses, respectively (101,106,107). For example, inhibiting SREBP signaling in Tregs can reduce tumor growth without causing autoimmune toxicity (108). Bariatric surgery, by ameliorating lipid metabolism, markedly reduces serum cholesterol levels, enhances the oxidative capacity of adipose tissue and promotes fatty acid oxidation and energy expenditure, thereby alleviating body weight and improving insulin sensitivity and overall metabolic health (109).

Glutamine metabolism modulation. Glutamine metabolism modulation is also a promising therapeutic strategy (110-113). Targeting glutamine metabolism in cancer cells and immune cells has shown potential in enhancing anti-tumor immunity. Inhibitors like JPH203 and DRP-104 can reduce glutamine uptake in tumor cells while enhancing $CD8^+$T cell infiltration and function (114,115). Additionally, upregulating glutamine metabolism in macrophages through CD40 activation can enhance their anti-tumor activity (104). Other metabolic pathways, such as serine metabolism and lactic acid metabolism, also hold therapeutic potential. Inhibiting serine synthesis in immune cells can enhance NK cell activation and improve the efficacy of immunotherapy (116). Lycorine, which reduces serine/glycine metabolites, has shown potential in eliminating leukemia cells (117). Modulating lactic acid transport in $CD8^+$T cells can enhance their anti-tumor activity (118). Lithium carbonate, for example, promotes lactic acid transport into mitochondria, improving T cell function (119). Based on a systematic review of the latest PubMed-indexed literature (120-130), the present review integrated the four metabolic pathways underlying 'post-weight-loss immune optimization' into an intervention roadmap ranked according to the following priorities. Metabolic pathways prioritization for post-bariatric immune optimization are shown in Table II.

Inflammatory pathways. In the context of obesity-associated chronic low-grade inflammation, both macrophages and T cells are prominently present within adipose tissue, exerting significant influence on the inception and propagation of inflammatory processes (18). Post-bariatric surgery, a notable regulatory shift occurs in macrophage function, characterized by a polarization transition from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. This transformation effectively curtails the generation of inflammatory cytokines (131).

Concurrently, the signaling pathways governing T cell behavior undergo substantial alterations (132). Specifically, the expression profiles of several key genes, including CXCR1, CXCR2, CCR7, IL7R and G-protein coupled receptor 97 (GPR97), are modulated. These genetic changes subsequently affect the activation and functional dynamics of T cells, thereby contributing to a mitigated inflammatory response (133).

Moreover, the cytokine IL-6, which exhibits a complex dual role in obesity-related inflammation, is subject to significant changes post-surgery (134). In obese individuals, elevated IL-6 levels are typically associated with heightened inflammation and insulin resistance (134). However, following bariatric intervention, the levels and functional attributes of IL-6 are reconfigured. The pro-inflammatory effects of IL-6 are attenuated, while its beneficial metabolic regulatory functions are preserved. Similarly, TNF-α, a pivotal pro-inflammatory cytokine intricately linked to obesity-associated inflammation and insulin resistance, experiences a marked reduction in concentration following bariatric surgery (135). This decline in TNF-α levels plays a crucial role in dampening the overall inflammatory cascade (135).

In individuals with obesity, visceral adipose tissue exhibits markedly augmented IL-16 expression, which is intimately intertwined with a state of smoldering, low-grade inflammation (136). Following bariatric surgery, IL-16 undergoes an early, transient surge; yet, as adiposity and body mass progressively wane, its concentrations regress to, or even below, pre-operative baselines. Immunomodulatory interventions that target IL-16 or its processing proteases could emerge as an adjunct anti-inflammatory strategy beyond bariatric surgery itself (137). Collectively, these dynamics intimate that bariatric surgery exerts an indirect but potent anti-inflammatory effect by alleviating the adipose-tissue burden, thereby dampening IL-16-driven inflammatory cascades, ameliorating metabolic homeostasis and mitigating post-surgical inflammatory sequelae (138).

In addition to these cellular and cytokine changes, the activity of key signaling pathways is also modulated. The Toll-like receptor signaling pathway, a primary initiator of inflammation in adipose tissue, is suppressed post-surgery, leading to a reduction in inflammatory cytokine production (139). The Janus kinase-signal transducer and activator of transcription signaling pathway, which is integral to the regulation of both adipose tissue inflammation and metabolic homeostasis, also undergoes functional alterations (140). These changes collectively contribute to the overall attenuation of the inflammatory response observed following bariatric surgical interventions.

Peculiarly, recent studies show that residual inflammatory 'imprints' can epigenetically reprogram innate and adaptive immunity, leading to long-term reductions in vaccine efficacy and immunotherapy success: Prior infection- or inflammation-induced suppressive programs persist for at least a month and hinder T-cell expansion and dendritic-cell priming, while repeated mRNA vaccination in a chronic inflammatory milieu sustains IFN-α/IL-6 signals that exacerbate inflammation and blunt subsequent therapeutic responses (141-143).

4. Targeted treatment methods

Targeted therapy of immune cell surface targets. Obesity is associated with IL-7Rα overexpression, which disrupts immune cell function (27). Targeting IL-7Rα with specific antibodies can stabilize T cells, reduce pro-inflammatory cytokines and control obesity-related inflammation (27). This approach is well-tolerated in healthy individuals and may be applicable to patients with obesity. Other immune cell surface molecules, such as CXCR1, CXCR2, CCR7, IL7R and GPR97, are also being explored as potential targets to enhance immune cell activation and function, thereby reducing inflammation (132).

Obesity also alters the gut microbiota and bariatric surgery can improve its composition (64). Supplementing

Table II. Metabolic pathway prioritization for post-bariatric immune optimization.

Authors, year	Stage	Time window	Priority metabolic pathway	Key molecular targets	Intervention	Dose/frequency	Expected immune benefit	Monitoring parameters	(Refs.)
Raud *et al*, 2018	Stage 1	0-2 weeks post-surgery	Fatty-acid β-oxidation (FAO)	AMPK, CPT1A, SIRT1	MCT or ω-3 PUFA	2-4 g/day	Stabilize Treg and $CD8^+$ Tem function	β-hydroxybutyrate, CPT1A mRNA	(120)
Ferraz-Bannitz *et al*, 2021; Hatami *et al*, 2024	Stage 1	0-2 weeks post-surgery	OXPHOS	PGC-1α, NRF2	Nicotinamide riboside (NR)	300 mg/day	Rapid recovery of NK-cell count	NAD^+/NADH ratio, NK-cell count	(121,122)
Vargas-Mendoza *et al*, 2019	Stage 1	0-2 weeks post-surgery	OXPHOS	PGC-1α, NRF2	Low-intensity endurance exercise	20 min, 3 times/week	Enhance mitochondrial biogenesis, reduce ROS	d-ROMs, PGC-1α mRNA	(123)
Lo *et al*, 2014	Stage 2	2-8 weeks post-surgery	Glycolysis	mTORC1, HIF-1α	Pulsed carbohydrate intake	<30 g per serving, 2 servings/day	Restore Th1/Th17 balance	Blood glucose, HIF-1α mRNA	(124)
Vargas-Mendoza *et al*, 2019; de Lange *et al*, 2023	Stage 2	2-8 weeks post-surgery	Glycolysis	mTORC1, HIF-1α	16/8 intermittent fasting	Daily	Cyclical mTOR activation	Insulin, lactate	(123,125)
Biobaku *et al*, 2020; Greto *et al*, 2021	Stage 2	2-8 weeks post-surgery	Glycolysis	mTORC1, HIF-1α	Rapamycin (optional)	1 mg/week	Prevent excessive inflammation	IL-6, CRP	(126,127)
Pribić *et al*, 2025	Stage 3	4-12 weeks post-surgery	Glutaminolysis	GLS, ASCT2	Glutamine supplementation	0.3 g/kg/day (only if plasma Gln low)	Replenish TCA intermediates, stabilize macrophages and Th17	Plasma glutamine, GLS activity	(128)
Haran *et al*, 2023; Kim *et al*, 2023	Stage 3	4-12 weeks post-surgery	OXPHOS	PGC-1α, NRF2	Maintain NR + endurance exercise	Same as Stage 1	Long-term immune memory consolidation	NK-cell count, IgG galactosylation index	(129,130)

FAO, fatty-acid β-oxidation; OXPHO, oxidative phosphorylation; AMPK, AMP-activated protein kinase; CPT1A, carnitine palmitoyltransferase 1A; SIRT1, sirtuin or silent mating type information regulation 2 homolog-1; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-α; NRF2, nuclear factor E2-related factor 2; mTORC-1, mammalian target of rapamycin complex 1; HIF-1α, hypoxia-inducible factor-1α; GLS, glutaminase; ASCT2, alanine-serine-cysteine transporter 2; TCA, tricarboxylic acid; Th17, t-helper 17 (cells); NR, nicotinamide riboside; NK-cell, natural killer cell; NAD^+/NADH, nicotinamide adenine dinucleotide/reduced nicotinamide adenine dinucleotide; ROS, reactive oxygen species; IL-6, interleukin-6; ω-3 PUFA, ω-3 polyunsaturated fatty acid; MCT, medium chain triglyceride; IgG, immunoglobulin G.

with specific probiotics, like those containing *Lactobacillus* and *Bifidobacterium* species, can further lower serum TNF-α levels and increase postoperative weight loss (64). Probiotics can modulate cytokine levels by increasing anti-inflammatory cytokines and decreasing pro-inflammatory cytokines, while simultaneously enhancing intestinal barrier function, reducing bacterial translocation and attenuating systemic inflammation (144,145). Additionally, metabolic reprogramming of immune cells following bariatric surgery, particularly shifting T cells and B cells from a pro-inflammatory to an anti-inflammatory state, may help alleviate chronic inflammation in obesity (118). Lastly, while inflammation is a necessary part of the body's defense against injury and infection, surgical procedures and the anesthetic agents used can either enhance or alter biomarkers (146,147). Evidence indicates that anesthesia modality markedly modulates perioperative immunity: A meta-analysis found propofol TIVA more effectively suppressed pro-inflammatory cytokines (IL-6, TNF-α) and elevated IL-10 than sevoflurane, while a hysterectomy trial showed spinal vs. general anesthesia further reduced postoperative IL-6, CRP and MDA while preserving antioxidant enzymes. Thus, both propofol over sevoflurane and spinal over general anesthesia confer immunoprotection by attenuating systemic inflammation and oxidative stress (146,147).

Targeted intracellular therapy. New progress has been made in the research of intracellular target therapy of immune cells following bariatric surgery. IL-27 enhances the anti-tumor function of $CD8^+$T cells and inhibits immune suppressor factors by activating the STAT1/3 signaling pathway (119). It also acts on adipocytes to promote the expression of uncoupling protein 1 via the p38MAPK/peroxisome proliferator-activated receptor γ coactivator 1-α pathway, thereby regulating obesity (18). In addition, the pro-inflammatory characteristics of circulating T cells in patients with obesity are improved following bariatric surgery, with the recovery of $CD4^+$ Treg cell levels and increased proliferation and activation of Tfh and B cells (4). The activation status and expression changes of immune checkpoint molecules in obesity-related T cell subsets may serve as potential targets (4). In a study, it was found that glutamate receptor scaffold proteins (PSD-95 and PICKL) were involved in the anchoring and transport of glutamate receptors and their PDZ domains have become therapeutic targets for various central nervous system diseases (148).

5. Conclusion and prospects

Bariatric surgery is no longer simply a mechanical restriction or malabsorptive procedure; it functions as a systems-level 'immuno-metabolic reboot'. By simultaneously correcting the chronic, low-grade inflammatory tone of obesity and re-wiring the bioenergetic circuitry of virtually every circulating immune subset, surgery converts pathologic adipose-immune cross-talk into a homeostatic dialogue that sustains weight loss and metabolic remission. Over the next decade, three converging developments will redefine post-surgical care, besides single-cell multi-omics and AI-driven trajectory mapping will allow real-time identification of patients who retain pro-inflammatory immune 'scars', enabling precision rescue therapy before weight regain or diabetes relapse occurs; pharmacologic fine-tuning of discrete metabolic checkpoints, glycolytic rate-limiting enzymes, OXPHOS modulators and glutamine/FAO switches, will be combined with microbiota-directed interventions to accelerate functional maturation of Treg, NK and antigen-presenting cell compartments and these same immuno-metabolic insights will be exported to oncology: Leveraging the bariatric-induced reduction in PD-1hi macrophages and MDSCs to convert the obesity-associated 'cold' tumor microenvironment into one that is highly responsive to immune-checkpoint blockade. Ultimately, bariatric surgery will evolve from a last-resort metabolic operation into a programmable gateway for lifelong immuno-metabolic precision medicine, delivering not just sustained weight loss, but durable protection against diabetes, cardiovascular disease and cancer.

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YS and KS were both responsible for the conception and writing of the present review. RY contributed to the design of the figures. HX contributed to literature search and collating references. CL was responsible for language editing and for critical revision and for making substantial contributions to conception and design. YD was responsible for preparing analysis and interpretation of data and stylistic refinement. YR and YZ were both in charge of the conception and design of the present review. Data authentication is not applicable. All authors read and approved the final manuscript.

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Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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